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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Shlomit Weizel et al.
Serial No.	:	10/016752
Filed	:	October 30, 2001
For	:	NOVEL CRYSTAL AND SOLVATE FORMS OF ONDANSETRON HYDROCHLORIDE AND PROCESSES FOR THEIR PREPARATION
Examiner	:	Taylor V. Oh
Art Unit	:	1625

Commissioner for Patents
P.O. Box 1450
Alexandria, Va 22313-1450

DECLARATION OF REVITAL LIFSHITZ UNDER 37 C.F.R. § 1.132

Sir:

I Revital Lifshitz, of 17 Hapalmach St., Apt. #1, Herzlia, Israel, declare as follows:

1. I graduated from the Chemistry school of Tel-Aviv university with a Masters degree in Organic synthesis in 1992. I have been a practicing chemist for 5 years.

2. I have worked for Teva Pharmaceutical Industries, Ltd. ("Teva") since August 16, 1998. I currently hold the position of project manager.

3. I am an inventor of U.S. Patent Application Serial No. 10/016752, captioned above, and am knowledgeable regarding its contents.

4. I have read the Office Action mailed January 6, 2003 and a copy of the English translation of Chinese Patent Application No. CN1113234A ("Wu Gousheng") that is the basis for the rejection of claims 1-4, 9, 19-23, 39-45, 49, 50, 52, 62, 67, 71, and 87-91 for lack of novelty.

5. Based upon my review of Wu Gousheng, it is my understanding that Embodiments A_1, A_2 and B produce ondansetron hydrochloride dihydrate ("compound X") by crystallization from water. In Embodiments A_1 and A_2, the dihydrate is dried in a dessicator over P_2O_5 under vacuum to yield ondansetron hydrochloride monohydrate.

6. I and my co-inventor Judith Aronhime were prompted by the January 6, 2003 Office Action to study the solid state characteristics of the monohydrate products of Embodiments A_1 and A_2.

7. I personally conducted the necessary preparations. I first prepared ondansetron hydrochloride dihydrate following the procedure of Embodiment B on an approximately 80 fold larger scale starting with ondansetron base. A description of the procedure I used and my observations is attached as an appendix. I prepared a 45.5 mg ml^{-1} solution of ondansetron in ethanol and then bubbled dry HCl gas through the solution until the solution had attained a pH of 2. I then cooled the solution in an ice bath, which caused ondansetron hydrochloride to precipitate. I collected the precipitate on a paper filter and washed it with ethanol. Then, I redissolved the precipitate in water to form a 0.8 g ml^{-1} solution and allowed the solution to stand at ambient temperature. Once a sufficient number of crystals had formed in the solution for powder X-ray diffraction and moisture content analysis, I collected the crystals on filter paper. I believe those crystals were ondansetron hydrochloride dihydrate, the reported product of Embodiment B of Wu Gousheng.

8. Following the drying procedures of Embodiments A_1 and A_2, I placed the ondansetron hydrochloride dihydrate crystals in a vacuum dessicator containing fresh phosphorous pentoxide (P_2O_5) and evacuated the dessicator to a pressure of 20 mbar. I consider this degree of vacuum to be conventional. Six hours later, I removed the crystals and they were analyzed for moisture content under my supervision. Duplicate analysis showed that they had a water content of 4.89 wt. %, which I believe to be in close agreement with the 5.177 wt. % theoretical water content of ondansetron hydrochloride monohydrate.

9. I gave samples of the crystals to my co-inventor Judith Aronhime to examine by powder X-ray crystallography.

10. I have read Judith Aronhime's declaration filed concurrently herewith. I confirm that the crystals she analyzed are the crystals whose preparation I have described in Paragraphs 7 and 8, above.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false stateements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 24.6.2003 Signed: _____

Revital Lifhitz

Appendix

A 1L three-necked round flask was loaded with 20g of ondansetron base and 440ml of absolute ethanol. The white slurry was heated to reflux temperature (78°C) to obtain almost complete dissolution. Then the oil bath was removed and HCl gas was bubbled into the suspension until pH=2. At this stage the reaction mixture became clear and colorless. The flask was cooled using an ice-bath to obtain a massive precipitation of OND·HCl. After stirring at room temperature for 25min, the product was isolated by filtration and washed with absolute ethanol (4x30ml) to obtain 50.4g of wet product.

The obtained wet OND·HCl (48g) was recrystallized from water (60ml) to obtain 11g of OND·HCl dihydrate. The obtained OND·HCl dihydrate was then dried in a desiccator under vacuum at RT in the presence of P_2O_5 for 6 hours until KF test showed 4.9%, which indicated monohydrate form.